10 Rec'd PCT/PTO 07 SEP 2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GERLI, Paolo
NOTARBARTOLO & GERVASI S.P.A.
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE

NOTARBARTOLO & GERVASI
MILANO
R E C E I V E D
28 GIU. 2004

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	24.06.2004
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
3068PTWO/AG/la	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/02204	07.03.2003	07.03.2002

Applicant
EURAND PHARMACEUTICALS LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hutterer, G Tel. +49 89 2399-8066

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3068PTWO/AG/a	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/02204	International filing date *(day/month/year)* 07.03.2003	Priority date *(day/month/year)* 07.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/14		
Applicant EURAND PHARMACEUTICALS LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.07.2003	24.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Toulacis, C Telephone No. +49 89 2399-8638

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/02204

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-10	as originally filed

Claims, Numbers

1-8	as originally filed
9-21	received on 17.05.2004 with letter of 14.05.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

V

Claims 1-21

(N) A process to load a drug into a cross-linked polymer comprising additionally to the steps (b) and © as they are defined in claim 1, a pre-treating step (a), is not disclosed in the documents cited in the search report.
The same applies to a method for increasing the drug-loading capacity of a cross-linked polymer comprising the treatment of the un-loaded polymer with a supercritical fluid according to claim 10.
The same applies to the modified cross-linked polymers as claimed in claim 16, being obtainable by a proccess according to claims 1-16 i.e. by pre-treating the sole cross-liked polymer as defined in claim 16, not containing any drug.

(IS) The object of the present application is to provide a process for loading a drug into a cross-linked polymer with supercritical fluid, which allows a higher degree of drug loading and more rapid kinetic of drug into cross-linked polymers (shorter process time) and higher thermodynamic activation than conventionally possible.
Said object has been achieved by pre-treating the cross-linked polymer with pure supercritical fluid followed by treatment with a supercritical fluid containing the drug dissolved therein (See examples 2 and 3).
The Applicant provides comparative examples showing the difference, by applying a process with and without the said pre-treatment.
Applying the pre-treatment step, I) a higher degree of drug loading, ii) a shorter process time (despite the pre-treatment step) and ii) a higher activation level (lower crystallinity) is obtained (see examples 2 and 3).
This is not suggested by the cited prior art documents.
Documents WO 01 68054 and WO 99 25322 (D3 and D4 respectively; representing the nearest prior art), disclose processes for impregnating a cross-linked polymer with an active ingredient with a supercritical fluid containing the drug, without pre-treatment with pure supercritical fluid.

(IA) The industrial applicability is beyond any doubt.

9. Process according to claims 1-8, further characterised in that the thus loaded drug is present in the cross-linked polymer in high amorphous and nanocrystalline fraction.

10. A method to increase the drug-loading capacity of a cross-linked polymer, consisting in treating said cross-linked polymer with a supercritical fluid not containing any drugs.

11. Method according to claim 10, wherein the cross-linked polymer is maintained in contact with the supercritical fluid for a time comprised between 1 minute and 6 hours.

12. Method according to claims 10-11, wherein the cross-linked polymer is maintained in contact with the supercritical fluid for a time comprised between 5 minutes and 4 hours.

13. Method according to claims 10-12, wherein the contact of the polymer with the supercritical fluid is effected in static and/or dynamic conditions.

14. Method according to claims 10-13, wherein the supercritical fluid is chosen among carbon dioxide, ethylene, propylene, chlorofluorocarbon, nitrous oxide, and mixtures thereof.

15. Method according to claims 10-14, wherein the cross-linked polymer is chosen among cross-linked polyvinylpyrrolidone, cross-linked cellulose derivatives, starch and its derivatives, cyclodextrins and their derivatives, cross-linked polystyrene, cross-linked acrylic polymers, and mixtures thereof.

16. Modified cross-linked polymer, having enhanced drug-loading properties, obtainable by treating a cross-linked polymer with a supercritical fluid not containing any drugs.

17. Modified cross-linked polymer according to claim 16, obtainable by treating the cross-linked polymer with the supercritical fluid for a time comprised between 1 minute and 6 hours.

18. Modified cross-linked polymer according to claims 16-17, obtainable by treating the cross-linked polymer with the supercritical fluid for a time comprised between 5 minutes and 4 hours.

19. Modified cross-linked polymer according to claims 16-18, wherein the supercritical fluid is chosen among carbon dioxide, ethylene, propylene, chlorofluorocarbon, nitrous oxide, and mixtures thereof.

20. Modified cross-linked polymer according to claims 16-19, wherein the cross-linked polymer to be modified is chosen among cross-linked polyvinylpyrrolidone, cross-linked cellulose derivatives, starch and its derivatives, cyclodextrins and their derivatives, cross-linked polystyrene, cross-linked acrylic polymers, and mixtures thereof.

21. Modified cross-linked polymer according to claims 16-20, loaded with a drug.

22. Pharmaceutical composition containing the modified cross-linked polymer described in claim 21.